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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

JIANG, SHAOJIA A

ART UNIT PAPER NUMBER

1617

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/993,976	Applicant(s) YATVIN ET AL.	
	Examiner Shaojia A Jiang	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11, 18 and 19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11, 18 and 19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/27/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 2, 2004 has been entered.

This Office Action is a response to Applicant's request for continued examination (RCE) filed April 2, 2004, and response/remarks to the Final Office Action (mailed October 2, 2003), filed April 2, 2004.

Currently, claims 1-11 and 18-19 are pending in this application.

Claims 1-11 and 18-19 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular and specific agent such as melatonin or serotonin conjugate with specific and particular spacer disclosed in the specification (see Figure 1 and Example 1 of the specification

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herein) in composition herein, does not reasonably provide enablement for any substances or compounds represented by “a psychotropic, neurotropic or neurological drug, or an antibiotic, antibacterial, antimycotic, antiviral, antiproliferative or antineoplastic drug, an amino acid or amino acid derivative specifically transported into a physiologically-protected site, two linker functional groups and a spacer, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first end of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group” recited in the claim 1 herein for example.

Even regarding the active agents recited in claims 2 and 19, a skilled artisan would clearly recognize that these agents are known to have separate and patentably distinct structures, possessing very different physical, chemical, biological and physiological properties or activities; moreover, they are classified in different subclasses of class 514. Thus, the specification while being enabling for the particular and specific agent such as melatonin or serotonin conjugate with specific and particular spacer disclosed in the specification, does not reasonably provide enablement for those agents or compounds recited in claims 2 and 19.

Note that any pharmaceutical agents represented by “a psychotropic, neurotropic or neurological drug, or an antibiotic, antibacterial, antimycotic, antiviral, antiproliferative or antineoplastic drug, an amino acid or amino acid derivative” broadly encompass those known and unknown compounds as of the instant filing date, as well as those future known compounds.

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The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a pharmaceutical composition for use the particular treatment.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims read on those known and unknown pharmaceuticals represented by "a psychotropic, neurotropic or neurological drug, or an antibiotic, antibacterial, antimycotic, antiviral, antiproliferative or antineoplastic drug, an amino acid or amino acid derivative" as of the instant filing date, as well as those future known compounds.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the

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recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, represented by "a psychotropic, neurotropic or neurological drug, or an antibiotic, antibacterial, antimycotic, antiviral, antiproliferative or antineoplastic drug, an amino acid or amino acid derivative", recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides those particular compounds for the composition.

Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

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The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., human) any compounds represented by "a psychotropic, neurotropic or neurological drug, or an antibiotic, antibacterial, antimycotic, antiviral, antiproliferative or antineoplastic drug, an amino acid or amino acid derivative" conjugated with a spacer recited having a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first end of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker

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functional group, broadly encompassing those known and unknown compounds, as well as those future known compounds, **requiring additional or future research to establish or verify their usefulness.**

See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added). In the instant case, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having claimed functional properties in the pharmaceutical compositions herein to be administered to a host. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable. The presence or absence of working examples and the quantity of experimentation necessary:

It is noted that only two particular agents, melatonin or serotonin conjugate with specific and particular spacer disclosed in the specification (see Figure 1 and Example

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1 of the specification herein). Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the active agents or compounds in the claimed composition. See MPEP § 716.02(d).

Thus, the specification fails to provide sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions and a spacer recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Therefore, in view of the Wands factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test all compounds encompassed in the instant claims and their combinations with a spacer in the claimed compositions to be administered to a host, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitations, "a physiologically-protected site, two linker functional groups and **a spacer**, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first end of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group" and "derivatives" render claims 1-11 and 18-19 indefinite. These recitations, are not clearly defined in the specification. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "a physiologically-protected site, two linker functional groups and **a spacer**, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first end of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group" and "derivatives", which could be many various structural groups with possibly numerous substituents. As a result, any significant structural variation to a compound would be reasonably expected to alter its properties, e.g., physiological effects and functions. Thus, it is unclear as to what compounds herein would be encompassed thereby.

Further, Claims 1, 4-5, 7, and 18 are rejected under the judicially created doctrine of an improper Markush group (Ex parte Hass, POBA 1975, 1888 USPQ 374). "The

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claimed compounds need only belong to a subgenus as defined by Applicant which is not repugnant to scientific classification (In re Harnisch, CCPA 1980, 631 F2d 716, 206 USPQ 300; Ex Parte Holt et al. POBA, 1982, 214 USPQ 381). The instant compounds recited in these claims do not belong to any recognized class of chemical compounds and therefore is repugnant to chemical classification. The Markush group is proper if "unity of invention" exists as evidenced by a **substantial structural feature** of the claimed compounds which is disclosed as essential to at least one disclosed utility (In re Hozumi, POBA 1984, 3 PQ2D 1059). The recitation in these claims is neither substantial nor shown to be essential by itself to the disclosed use. The propriety of a substituent on a compound being defined by a Markush expression is determined by a consideration of the compounds as a whole. Thus, defining substituents Markush-wise is proper when the claimed compounds have a common nucleus which would exhibit certain characteristics irrespective of the nature of these substituents (Ex parte Holt et al. supra; Ex parte Taylor, POBA 1969, 167 USPQ 637). The instant Markush group lacks of the core for definition or characteristics which are significant. Further, the instant generic structure presented creates difficulty in using as prior art if allowed to issue, since it is impossible to ascertain the true chemical structure in the instant claimed composition.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5, 7-9 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Yatvin et al. (US 5,149,794) for reasons of record stated in the Office

Action dated October 2, 2003.

Yatvin et al. discloses a pharmaceutical composition comprising an antiviral or an anti proliferative or antineoplastic drug, and two linker functional groups and a spacer, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group (see particularly Fig.1-8; Examples 1-8; claims 1 and 7). Yatvin et al. also discloses that the instant spacer allows the drug to act without being released at an intracellular site or allows the facilitated hydrolytic release of the drug at an intracellular site wherein the first linker functional group attached to the first end of the spacer is strong and the second linker functional group attached to the second end of the spacer is weak (see particularly claims 2-3 therein). Yatvin et al. also discloses that the instant first functional linker group is a hydroxy group, a primary or secondary amino group a phosphate group or a carboxylic acid group (see claims 8-9) and that the instant spacer is a peptide for (amino acid) n formula (see claim 6).

Thus, Yatvin et al. anticipates Claims 1, 3-5, 7-9 and 18.

Applicant's remarks filed on April 2, 2004 with respect to this rejection made under 35 U.S.C. 102(b) in the previous Office Action have been fully considered but they are not deemed persuasive to render the claimed invention patentable over the prior art for the following reasons.

Again, Applicant asserts that Yatvin et al. (US 5,149,794) uses only lipids attached to a drug for site specific drug delivery. Contrary to Applicant's assertion, as discussed in the previous Office Action, Yatvin (US 5,149,794) discloses a pharmaceutical composition comprising an antiviral or an anti proliferative or antineoplastic drug, a polar lipid carrier, and two linker functional groups and a spacer, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative i.e., tBc-NHAla-Ala- or -Gly-Gly-Gly-Gly-NH-, is attached to the first of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group (see particularly Fig.1-8; Examples 1-8; claims 1 and 7). Moreover, Yatvin clearly discloses that the instant spacer is a peptide for (amino acid)_n formula, a polymer of a particular amino acid (see claim 6 in particular) i.e., tBc-NHAla-Ala- or -Gly-Gly-Gly-Gly-NH-.

Thus, Yatvin et al. anticipates Claims 1, 3-5, 7-9 and 18.

Claims 1-5, 7-9, 11 and 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Yatvin et al. (US 5,543,389) for reasons of record stated in the Office Action dated October 2, 2003.

Yatvin et al. discloses a pharmaceutical composition comprising an antiviral or an antiproliferative drug such as the particular drug, methotrexate, and two linker functional groups and a spacer, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group (see particularly Fig.1; Example 1; claims 1-24). Yatvin et al. also discloses that the instant spacer allows the drug to act without being released at an intracellular site or allows the facilitated hydrolytic release of the drug at an intracellular site wherein the first linker functional group attached to the first end of the spacer is strong and the second linker functional group attached to the second end of the spacer is weak (see particularly claims 10-11 therein). Yatvin et al. also discloses that the instant first functional linker group is a hydroxy group, a primary or secondary amino group a phosphate group or a carboxylic acid group (see claims 19-21) and that the instant spacer is a peptide for (amino acid)_n formula (see claim 13). Thus, Yatvin et al. anticipates Claims 1-5, 7-9, 11 and 18-19.

Applicant's remarks filed on April 2, 2004 with respect to this rejection made under 35 U.S.C. 102(b) in the previous Office Action have been fully considered but they are not deemed persuasive to render the claimed invention patentable over the prior art for the following reasons.

Again, Applicant asserts that Yatvin et al. (US 5,543,389) uses only lipids attached to a drug for site specific drug delivery. Contrary to Applicant's assertion,

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Yatvin (US 5,543,389) discloses a pharmaceutical composition comprising an antiviral or an anti proliferative or antineoplastic drug, a polar lipid carrier, and two linker functional groups and a spacer, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group (see particularly Fig.1; Example 1; claims 1-24); in particular Yatvin clearly discloses that the instant spacer is a peptide for (amino acid)_n formula, a polymer of a particular amino acid (see claim 13) as discussed in the previous Office Action.

Thus, Yatvin et al. anticipates Claims 1-5, 7-9, 11 and 18-19.

Claims 1-5, 7-9, 11 and 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Yatvin et al. (US 5,827,819) for reasons of record stated in the Office Action dated October 2, 2003.

Yatvin et al. discloses a pharmaceutical composition comprising a psychotropic, neurotropic or neurological drug such as the particular instant drugs, for example L-dopa, hydroxytryptamine, amantadine, benztropine, and levadopa (see in particular claim 2 and 11), and two linker functional groups and a spacer, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group (see particularly Fig.1-6; Example 1-6; claims 1-12). Yatvin et al. also discloses that the

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instant spacer allows the drug to act without being released at an intracellular site or allows the facilitated hydrolytic release of the drug at an intracellular site wherein the first linker functional group attached to the first end of the spacer is strong and the second linker functional group attached to the second end of the spacer is weak (see particularly claims 4-5 therein). Yatvin et al. also discloses that the instant first functional linker group is a hydroxy group, a primary or secondary amino group a phosphate group or a carboxylic acid group (see claims 7-9) and that the instant spacer is a peptide for (amino acid)_n formula (see claim 12). Thus, Yatvin et al. anticipates Claims 1-5, 7-9, 11 and 18-19.

Applicant's remarks filed on April 2, 2004 with respect to this rejection made under 35 U.S.C. 102(b) in the previous Office Action have been fully considered but they are not deemed persuasive to render the claimed invention patentable over the prior art for the following reasons.

Again, Applicant asserts that Yatvin et al. (US 5,827,819) uses only lipids attached to a drug for site specific drug delivery. Contrary to Applicant's assertion, Yatvin (US 5,827,819) discloses a pharmaceutical composition comprising an antiviral or an anti proliferative or antineoplastic drug, a polar lipid carrier, and two linker functional groups and a spacer, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group (see particularly Fig.1-6; Example 1-6;

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claims 1-12); in particular Yatvin clearly discloses that the instant spacer is a peptide for (amino acid)_n formula, a polymer of a particular amino acid (see claim 12) as discussed in the previous Office Action.

Thus, Yatvin et al. anticipates Claims 1-5, 7-9, 11 and 18-19.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 6 and 10, even though these claims are not anticipated by Yatvin et al. (US 5,149,794) as applicable to claims 1, 3-5, 7-9 and 18, are rejected under 35 U.S.C. 103(a) as being unpatentable over the same reference by Yatvin et al. for reasons of record stated in the Office Action dated October 2, 2003.

The same disclosure of Yatvin et al. in 5,149,794 has been discussed above (see *supra*).

Yatvin et al. does not expressly disclose the employment of the particular amino acid or derivative herein in the composition therein.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular amino acid or derivative herein in the composition therein.

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One having ordinary skill in the art at the time the invention was made would have been motivated employ the particular amino acid or derivative herein in the composition therein since amino acid derivatives such as peptide broadly are known to be employed in the compositions of Yatvin et al. Moreover, one of ordinary skill in the art would clearly acknowledge that amino acid and its derivatives broadly possess at least two functional groups which can be linked to other a hydroxy group, a primary or secondary amino group a phosphate group or a carboxylic acid group. Therefore, one of ordinary skill in the art would have found it obvious to employ the particular known amino acid or derivative herein having the same or similar functional in the compositions of Yatvin et al.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks filed on April 2, 2004 with respect to this rejection made under 35 U.S.C. 103(a) of record in the previous Office Action have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art for the following reasons.

Again, Applicant asserts that Yatvin et al. (US 5,149,794) uses only lipids attached to a drug for site specific drug delivery. As discussed above, Yatvin (US 5,149,794) clearly discloses that the instant spacer is a peptide for (amino acid)_n formula, a polymer of a particular amino acid (see claim 6 in particular) i.e., tBc-NHAla-Ala- or -Gly-Gly-Gly-Gly-NH-. Further, as discussed in the previous Office Action,

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therefore, one of ordinary skill in the art would have found it obvious to employ the particular known amino acid or derivative herein having the same or similar functional in the compositions of Yatvin et al.

Further, the record contains no clear and convincing evidence of unexpected results for the claimed invention herein over the prior art. In this regard, it is noted that the specification provides no side-by-side comparison with the closest prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-5, 7-9 and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S.

Patent No. 5,149,794 for reasons of record stated in the Office Action dated October 2, 2003.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent are drawn to a pharmaceutical composition

comprising an antiviral or an anti proliferative or antineoplastic drug, and two linker functional groups and a spacer, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group (see particularly Fig.1-8; Examples 1-8; claims 1 and 7). Yatvin et al. also discloses that the instant spacer allows the drug to act without being released at an intracellular site or allows the facilitated hydrolytic release of the drug at an intracellular site wherein the first linker functional group attached to the first end of the spacer is strong and the second linker functional group attached to the second end of the spacer is weak (see particularly claims 2-3 therein). Yatvin et al. also discloses that the instant first functional linker group is a hydroxy group, a primary or secondary amino group a phosphate group or a carboxylic acid group (see claims 8-9) and that the instant spacer is a peptide for (amino acid)_n formula.

Thus, the instant claims 1, 3-5, 7-9 and 18 are seen to be anticipated by the claims 1-10 of U.S. Patent No. 5,149,794.

Claims 1-5, 7-9, 11 and 18-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 5,543,389.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent are drawn to a pharmaceutical composition comprising an antiproliferative drug such as the particular drug, methotrexate, and two

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linker functional groups and a spacer, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group (see particularly Fig.1; Example 1; claims 1-24). Yatvin et al. also discloses that the instant spacer allows the drug to act without being released at an intracellular site or allows the facilitated hydrolytic release of the drug at an intracellular site wherein the first linker functional group attached to the first end of the spacer is strong and the second linker functional group attached to the second end of the spacer is weak (see particularly claims 10-11 therein). Yatvin et al. also discloses that the instant first functional linker group is a hydroxy group, a primary or secondary amino group a phosphate group or a carboxylic acid group (see claims 19-21) and that the instant spacer is a peptide for (amino acid)_n formula (see claim 13).

Thus, the instant claims 1-5, 7-9, 11 and 18-19 are seen to be anticipated by the claims 1-27 of U.S. Patent No. 5,543,389.

Claims 1-5, 7-9, 11 and 18-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,827,819 for reasons of record stated in the Office Action dated October 2, 2003.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent are drawn to a pharmaceutical composition comprising a psychotropic, neurotropic or neurological drug such as the particular instant

drugs, for example L-dopa, hydroxytryptamine, amantadine, benztropine, and levadopa (see in particular claim 2 and 11), and two linker functional groups and a spacer, wherein the spacer has a first end and a second end and wherein the amino acid or amino acid derivative is attached to the first of the spacer through a first linker functional group and the drug is attached to the second end of the spacer through a second linker functional group (see particularly Fig.1-6; Example 1-6; claims 1-12). Yatvin et al. also discloses that the instant spacer allows the drug to act without being released at an intracellular site or allows the facilitated hydrolytic release of the drug at an intracellular site wherein the first linker functional group attached to the first end of the spacer is strong and the second linker functional group attached to the second end of the spacer is weak (see particularly claims 4-5 therein). Yatvin et al. also discloses that the instant first functional linker group is a hydroxy group, a primary or secondary amino group a phosphate group or a carboxylic acid group (see claims 7-9) and that the instant spacer is a peptide for (amino acid)_n formula (see claim 12).

Thus, the instant claims 1-5, 7-9, 11 and 18-19 are seen to be anticipated by the claims 1-12 of U.S. Patent No. 5,827,819.

Applicant's remarks filed on April 2, 2004 with respect to these three obviousness-type double patenting rejections of record in the previous Office Action have been fully considered but are not deemed persuasive. These remarks are believed to be adequately addressed by the three rejections under 35 U.S.C. 102(b) as being anticipated by the same patents of Yatvin et al. above.

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In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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